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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/520,239	07/18/2005	Peter John Sadler	14084-005US1 / RJW/CP6263	5058
23575	7590	02/13/2009	EXAMINER	
CURATOLO SIDOTI CO., LPA 24500 CENTER RIDGE ROAD, SUITE 280 CLEVELAND, OH 44145			CHANDRAKUMAR, NIZAL S	
			ART UNIT	PAPER NUMBER
			1625	
			MAIL DATE	DELIVERY MODE
			02/13/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary

Application No.

10/520,239

Applicant(s)

SADLER ET AL.

Examiner

NIZAL S. CHANDRAKUMAR

Art Unit

1625

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 10/30/2008.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 26-45 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 26-45 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
 - ☐ Certified copies of the priority documents have been received in Application No. _____.
 - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☐ Information Disclosure Statement(s) (PTO/SF/ICE)
Paper No(s)/Mail Date _____
- 4) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date _____
- 5) ☐ Notice of Informal Patent Application
- 6) ☐ Other: _____

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 10/30/2009 has been entered.

Claims 26-45 are pending.

Response to Applicants Arguments:

Election/Restrictions

Applicants cancelled claims to non-elected group are cancelled. Instant claims relate to originally presented Group II.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 26-45 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which

applicant regards as the invention. Previously presented rejection is maintained for reasons of record. Additional reasons for the rejections are also presented along with response to applicants arguments.

The description of the instant formulae is replete with technical incongruity to such an extent that a meaningful assessment of the protection sought for, is impossible.

Amendments to claims deleting "a" from the description of the Y-L-Y' is insufficient to overcome the previously presented rejections. Applicants arguments are limited to "a". Office action 07/10/2007 recommends explicit structural delineation (see page 9, second paragraph, last sentence).

Some examples of technical issues with the instant description are shown below:

Variable X: The nature of X in the formula is unclear in spite of the definition of this variable in paragraph [0016] of the specification. Extending the definition of Y-L-Y' to mean that X is neutral or negatively charged when X is 'not present in the complex' (see [0042]) would mean species such as alkoxides when X is O; however, X negatively charged when present in the complex would mean ruthenium oxide with negative charge on oxygen. Also see page 4 of office action filed 04/30/2008 for related discussion pertaining to electrical charges.

Variable Y-L-Y': The definition of L defies art recognized concepts of chemical bonding and valency. What is the structure of L when C1 alkynylene? What is the structure of a Ru complex when Y-L-Y' is O-C2alkylene-O? (See below for discussion relating to the 'possession' aspect of such impossible structures). Is there a limit to the size of the ring system which includes Ru as one of the ring members? The position of

attachment and 'satisfaction' of valency requirements for the optional substituents on the L variables are vague and indefinite. It is unclear if a term is missing before the term 'ferrocenylene'. As such it is unclear if ferrocenylene and the articles listed after ferrocenylene are possibilities for L. Assessment of enablement requirements (USC 112-1) with regards to these variables will not be made in this office action because of the lack clarity. If Se is a possibility for L, then it would require unknown Y-Se-Y' species for making the complex. Alternately, Se as an optional substituent on the articles defined proceeding the term 'ferrocenylene' would violate accepted valency number for Se. As stated earlier, these above discussion are examples of impossible situations. Many if not most of the instantly claimed substituents are impossible because of problems with valency and hybridization which are fundamental concepts in chemistry. For example, a sp hybridization for carbons as required for a C2-alkynylene L variable would mean an impossible structure.

If a substituent is impossible, the claim can properly be rejected under 35 USC paragraph 1 or 2. A compound with an impossible substituent clearly cannot be made, and hence a paragraph 1 rejection is proper. Alternatively, if it is impossible, then it is not correct.

Applicant is reminded of *In re Zletz*, 13 USPQ2d 1320, 1322, "An essential purpose of patent examination is to fashion claims that are precise, clear, correct and unambiguous."

Redefinition of Y-L-Y' to limit the claims to Ru complexes derived from beta-dicarbonyl compounds would overcome the above rejection.

Claim Rejections - 35 USC § 112

Previously presented rejection under 35 U.S.C. 112, first paragraph is withdrawn in view of applicant's persuasive arguments and the following new rejection.

The following rejection is based on claim interpretation limited by the vague and indefinite nature of the instant claims. See rejection under 35 U.S.C. 112, second paragraph

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 26-45 rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for making few compounds of formula wherein Y-L-Y' is derived from beta-dicarbonyl compounds, does not reasonably provide enablement for the over abundance of structural possibilities encompassed by the claims. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make (and use) the invention commensurate in scope with these claims. The determination that "undue experimentation" would have been needed to make and use the claimed invention is not a single, simple factual determination. Rather, it is a conclusion reached by weighing all the relevant factual considerations.

Enablement is considered in view of the Wands factors (MPEP 2164.01 (a)). These include: (1) breadth of the claims; (2) nature of the invention; (3) state of the prior art; (4) amount of direction provided by the inventor; (5) the level of predictability in the art; (6) the existence of working examples; (7) quantity of experimentation needed to make or use the invention based on the content of the disclosure; and (8) relative skill in the art.

All of the factors have been considered with regard to the claims, with the most relevant factors discussed below:

The nature of invention is that the compounds of the instant formula bind to DNA and thus provide compounds that exhibit activity to tumor cells. In particular, these compounds are 'capable of binding to different DNA bases', presumably, the 'different bases' possibility is provided by the structural difference in the laundry list of substituents defined for the formula. As discussed below there is very enabling support in the specification for such a 'capability'.

The claims are drawn to compounds of formula with substituents layered on top of substituents encompassing zillions of conceivable structures that vary widely in physical and chemical properties such as size, molecular weight, logP, acidity, basicity, disposition of variables etc. These factors, known in the art to greatly influence biological properties, because of their wide nature, render the breadth of the claims large.

The chemistry direction provided in the specification for **making** the claimed compounds is extremely limited. The direction, working examples and guidance

provided in the specification for making compounds is limited to Y-L-Y' being beta-dicarbonyl derivatives. The prior art teaching is also limited to the same beta-dicarbonyl linkage for Y-L-Y'. That is, the specification fails to provide citations (commercial or literature) for procuring starting materials Y-L-Y' (other than beta-dicarbonyls) required for reacting with $[\pi 6-C6(R1)(R2)(R3)(R4)(R5)(R6))RuX2]$ to make the claimed Ru compounds. This assumes the later RuX2 pi-complexes are makeable with the laundry lists of substituents. Applicants remarks filed 10/30/2009 page 17, quotes MPEP, requiring explanation for doubting the truth or accuracy of the statement in the specification. The claims are drawn to structures impossible even to conceive and there is no disclosure in the prior art or in the specification for making anything other than complexes derived from negatively charged beta-dicarbonyl compounds. Further explanation of the 'doubt' is held in abeyance pending the clarification of variables as found under section 35 U.S.C. 112, second paragraph. However, based on the disclosure in the specification and the prior art, it is the Examiner's position, that at the time of the instant application, the applicant did not have in possession Ru complexes of the instantly claimed formula wherein Y-L-Y' is other than beta-dicarbonyl derivatives. The statement on page 20, second paragraph, last sentence regarding skilled workers ability to make any compounds contradicts the state of the organic chemical art. The unpredictability of in organic synthesis is high in spite of the high skill level in the area. The state of the art of organic chemical synthesis is closer to what is described by Dorwald et al. who states, "Most non-chemists would probably be horrified if they were to learn how many attempted syntheses fail, and how inefficient research chemists are.

The ratio of successful to unsuccessful chemical experiments in a normal research laboratory is far below unity, and synthetic research chemists, in the same way as most scientists, spend most of their time working out what went wrong, and why. Despite the many pitfalls lurking in organic synthesis, most organic chemistry textbooks and research articles do give the impression that organic reactions just proceed smoothly and that the total synthesis of complex natural products, for instance, is maybe a labor-intensive but otherwise undemanding task. In fact, most syntheses of structurally complex natural products are the result of several years of hard work by a team of chemists, with almost every step requiring careful optimization. The final synthesis usually looks quite different from that originally planned, because of unexpected difficulties encountered in the initially chosen synthetic sequence. Only the seasoned practitioner who has experienced for himself the many failures and frustrations which the development (sometimes even the repetition) of a synthesis usually implies will be able to appraise such work.....Chemists tend not to publish negative results, because these are, as opposed to positive results, never definite (and far too copious) [preface].....even structurally simple compounds often turn out not to be so easy to make as initially thought. [pg. 2]..... As illustrated by the examples discussed below, a good retrosynthesis requires much synthetic experience, a broad knowledge of chemical reactivity, and the ability to rapidly recognize synthetically accessible substructures [pg. 3]..... As will be shown throughout this book, the outcome of organic reactions is highly dependent on all structural features of a given starting material, and unexpected products may readily be formed. [8].....Even the most

experienced chemist will not be able to foresee all potential pitfalls of a synthesis, especially so if multifunctional, structurally complex intermediates must be prepared. The close proximity or conformational fixation of functional groups in a large molecule can alter their reactivity to such an extent that even simple chemical transformations can no longer be performed. Small structural variations of polyfunctional substrates might, therefore, bring about an unforeseeable change in reactivity [pg. 9]....." Dorwald F. A. Side Reactions in Organic Synthesis, 2005, Wiley: VCH, Weinheim pg. IX of Preface pg. 1-15.

Disclosure with respect to potential **'use aspect'** of the enablement requirement is limited to in vitro activities of the beta-dicarbonyl derivatives. Since cell line activity has been correlated to anti-cancer activity in the prior art, it can be acknowledged that the compounds of this ilk would have some utility. However, the micromolar potency (IC₅₀) of the instantly disclosed compounds would question whether these *particular* compounds would have any real world utility. There is no teaching in the specification that would direct and guide one skilled in the art to pick a potentially active compound from the zillions of structures claimed. This is because not only the 'active' structures disclosed all fall within a narrowly definable formula but also the disclosed 'active' compounds have shown wide differences in potency (IC₅₀s), ranging from inactive to >100 micromolar. Thus there is no structural guidance to pick substituents that would provide an embodiment that will have at least cell line activity. Further, the wide breadth of the claims defies art recognized concepts relating to productive small molecule-macromolecule interaction and finds little support in the specification. For the

reasons presented above, there is a substantial gap between what is taught in the specification and what is being claimed. Consequently, it is not clear what specific embodiments would be required for compounds to render them 'capable of binding to different DNA bases" (see paragraph [0012]) and thus provide compound that exhibits increased activity to drug-resistant tumor cells. Preceding this paragraph relating to the objective of the invention, the specification provides (by citations to prior art teachings) structural guidance for making compounds that are partial to binding to guanine bases. However, it is not seen where in the specification such structural guidance is found for selecting embodiments that would be partial to other DNA bases. As such, one of ordinary skill in the art would be faced with undue amount of experimentation to identify compound(s) buried in the zillion possibilities encompassed by the formula. The specification lacks disclosure sufficient to make and use the invention commensurate with the scope of the claims.

MPEP 2164.01(a) states, "A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. *In re Wright*, 999 F.2d 1557,1562, 27 USPQ 2d 1510, 1513 (Fed. Cir. 1993)." That conclusion is clearly justified here. Thus, undue experimentation would be required to make and use Applicants' invention.

Genentech Inc. v. Novo Nordisk A/S (CA FC) 42 USPQ2d 1001, states "a patent is not a hunting license. It is not a reward for search, but compensation for

its successful conclusion” and “[p]atent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable”.

Redefinition of Y-L-Y' to limit the claims to Ru complexes derived from beta-dicarbonyl compounds would overcome the above rejection.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

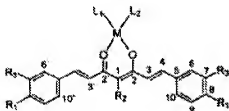
A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 26 and dependent claims 27-45 rejected under 35 U.S.C. 102(b) as being anticipated by prior art.

Kuhlwein et al. (Z. anorg. allg. Chem. 623 (1997) 1211-1219) teach

M = Ru



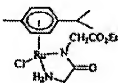
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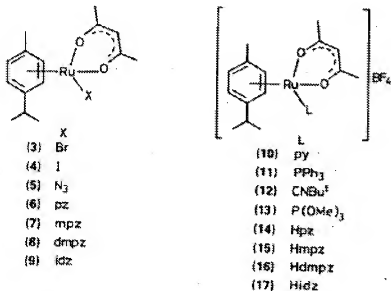
corresponding to compounds of the instant formula wherein L2 is X = halo, Cl; Y = Y' = O; L is alkenylene. L1 is p-cymol same as the only instantly enabled R1 to R6 substituted arene of the instant formula.

Likewise

Kramer et al *Chem. Euro. J.* 1 1996, 2 (12), 1518-1526)

teach

Everaere et al. *Eur. J. Org. Chem.* 2001, 2750291Carmona et al. (*J.Chem Soc. Dalton Trans.* 1990, 1463-1476) teach



Note: A compound and its properties are inseparable. A preamble is generally not accorded any patentable weight where it merely recites the purpose of a process or the intended use of a structure, and where the body of the claim does not depend on the preamble for completeness but, instead, the process steps or structural limitations are able to stand alone. See *In re Hirao*, 535 F.2d 67, 190 USPQ 15 (CCPA 1976) and *Kropa v. Robie*, 187 F.2d 150, 152, 88 USPQ 478, 481 (CCPA 195).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 26-45 rejected under 35 U.S.C. 103(a) as being unpatentable over Morris et al. WO 2001030790 in view of Kuhlwein et al. (Z. anorg. allg. Chem. 623 (1997) 1211-1219) , Kramer et al *Chem. Euro. J.* 1 1996, 2 (12), 1518-1526), Everaere et al. Eur. J. Org. Chem. 2001, 275-291 and Carmona et al. (J.Chem Soc. Dalton Trans. 1990, 1463-1476).

Morris et al. teach Ru complexes containing bidentate ligands wherein the bidentate ligand forms a ring system including Ru metal.

Morris et al. does not teach the instantly claimed cyclic Ru complexes in which the bidentate ligand is negatively charged.

(The instant definition, as found in [0042], of the bidentate ligand Y-L-Y' is vague and indefinite. The rejection is based on one of many possible interpretations.)

The instant formula encompasses compounds taught in the non-patent references, see rejection under 35 U.S.C. 102 (b). As such, one skilled in the art of medicinal chemistry at the time of the instant application, is well aware of Ru complexes containing negatively charged bidentate ligands. As routine practice in medicinal chemistry art, one skilled would be motivated to test all available Ru complexes in

searching for additional derivatives of Ru complexes taught by Morris et al. and would arrive at the instantly claimed compounds with reasonable expectation of success. Obviousness based on similarity of structure and functions entails motivation to make the claimed compound in expectation that compounds of similar in structure will have similar properties; therefore, one of ordinary skill in the art would be motivated to make the claimed compounds in searching for new compounds.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to NIZAL S. CHANDRAKUMAR whose telephone number is (571)272-6202. The examiner can normally be reached on 8.30 AM - 4.30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Janet Andres can be reached on 571 0272-0867. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Nizal S. Chandrakumar

/D. Margaret Seaman/

Primary Examiner, Art Unit 1625